

III

CONGENITAL SYPHILITIC MESAORTITIS ASSOCIATED WITH ACUTE YELLOW ATROPHY OF THE LIVER

WITH A NOTE ON THE SALVARSAN-LIVER NECROSIS SEQUENCE

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CLINICAL HISTORY

THE patient, M.C., a male aged nine, was admitted to the V.D. treatment centre, Royal Victoria Infirmary, Newcastle-upon-Tyne, on July 3rd, 1931, for interstitial keratitis due to congenital syphilis. The father had been under treatment for tertiary syphilis since 1925, and the mother had a history of still-births and early death of children.

Treatment was carried out as follows: Five 0.15 gm. doses of Novarsenobillon were given intravenously at regular intervals between July 30th and September 24th, 1931. The patient weighed 4 st. 2½ lb. at the commencement of treatment, and 4 st. 6½ lb. at the last injection. The eye symptoms improved and the general health appeared to be satisfactory.

On October 14th, 1931, the patient was re-admitted in a semi-comatose condition. Deep general jaundice was present, and there were petechiæ over the trunk. The child exhibited fits of restlessness associated with loud crying. Symptoms had apparently commenced three days before admission. The temperature was 104.8° F., and the pulse rate 128. The tongue and mouth were dry and foul. The liver dulness was markedly diminished, only the upper third being perceptible. There was considerable stiffness of the neck and rigidity of the back passing into fits of opisthotonus. During these attacks Cheyne-Stokes breathing was observed. There was a double extensor Babinski response and the abdominal

BRITISH JOURNAL OF VENEREAL DISEASES

reflexes were absent. Examination of the urine showed the following: Specific gravity 1022; albumen nil; bile +; acetone +++; sugar nil. No examination for leucine and tyrosine crystals was made. The clinical diagnosis was acute yellow atrophy of the liver. The patient sank rapidly and died ten hours after admission.

PATHOLOGICAL INVESTIGATION

An autopsy (Ref. 359/31) was performed on October 15th, 1931, fourteen hours after death.

External Examination.—Deep general icterus; numerous petechiæ on trunk and arms. No superficial signs of syphilis other than keratitis.

Sectio.—Thymus not enlarged. No pneumonia. No pericarditis. Heart not enlarged; weight 120.5 gm.; no endocarditis; numerous petechiæ over epicardium at base and beneath endocardium of left ventricle; myocardium bile stained and friable from toxic change. Pulmonary artery healthy.

For a distance of 2.5 cm. above the aortic cusps the intima of the first part of the aorta showed gross changes suggestive of syphilis (Fig. 1). There was marked wrinkling and roughening of the intima, and longitudinal fissures alternated with pearly flattened nodosities. The change was maximal above the left posterior aortic cusp. The aorta was very slightly dilated in this region and on section its wall was definitely thickened. There was no actual aneurysmal bulging. The coronary arteries, the thoracic and abdominal aorta and the iliac arteries showed no gross abnormality.

No peritonitis. Numerous subperitoneal petechiæ in mesentery and appendices epiploicæ. Mesenteric lymph nodes congested. The liver was greatly diminished in size and weighed 567 gm. The right lobe was 5 cm. above the costal margin and the left lobe extended for a distance of 3 cm. below the xiphisternum. There was no perihepatitis. The capsule was somewhat wrinkled and the organ was flabby to the touch. The surface was ochre-yellow in colour for the most part, but blotchy hæmorrhagic areas were present over the superior and posterior aspects of the right lobe, and to a lesser extent over the caudate lobe, tuber omentale and superior and posterior aspects of the left lobe. The surface was smooth. The

CONGENITAL SYPHILITIC MESAORTITIS

lymph nodes at the portal fissure were enlarged, bile-stained and acutely congested. The gall-bladder and bile ducts were healthy. On section, an opaque yellowish fluid could be scraped from the surface. The greater portion of the right lobe had a mottled red-yellow appearance, patchy in distribution (Fig. 2). The outlines of the lobules were obscured in many places; in others the shrunken and congested Glisson's capsule surrounded red necrotic areas. The appearances in the major part of the left lobe suggested fatty metamorphosis rather than necrosis, the lobular design being well preserved. There

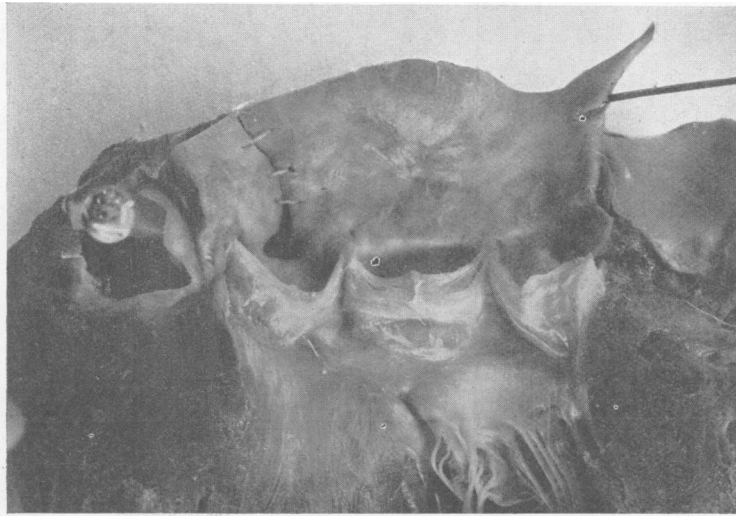


FIG. 1.—First part of aorta showing syphilitic lesions $\times \frac{1}{8}$.

was definite fibrosis of the portal tracts, the appearances due to shrinkage of liver substance having been allowed for. The spleen was slightly enlarged. On section the pulp was intensely congested and was fairly firm in consistency. The Malpighian bodies were prominent. The suprarenals and pancreas showed nothing abnormal save bile-staining, congestion and marked œdema. The kidneys were slightly enlarged, but showed only changes attributable to jaundice and toxæmia. The urinary bladder was distended with bile-stained urine. The stomach contained a small amount of food coloured with altered blood, and apart from submucosal petechiæ nothing abnormal was found in stomach and intestines.

BRITISH JOURNAL OF VENEREAL DISEASES

The testes and epididymes appeared normal. The right knee joint showed no evidence of arthritis and the upper epiphysis of the right fibula was healthy.

On removing dura mater a slight general flattening of the cerebral cortex was noted. There was no meningitis over vertex or base of brain. Section of the brain and cord showed nothing abnormal save oedema and a few petechiæ.

An anatomical diagnosis of acute liver necrosis, syphilitic aortitis and interstitial keratitis was made.

Portions of the following tissues were fixed in Helly's solution: Thymus, left ventricle, first part of aorta,

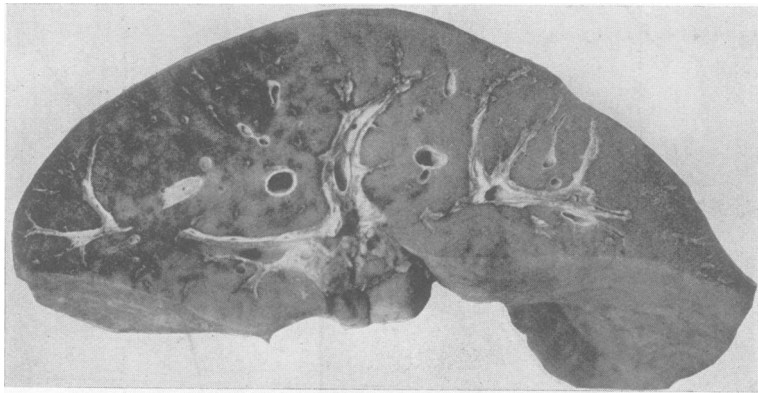


FIG. 2.—Liver (about 7/11 natural size) showing acute necrosis with fatty metamorphosis, and thickening of portal tracts.

pulmonary artery, right lung root and base, liver, lymph node from portal fissure, spleen, stomach, pancreas, left suprarenal, left kidney, mesenteric lymph node, superior mesenteric artery, right testis and epididymis, upper epiphysis of right fibula. Frozen sections were also prepared from the liver. The stains employed were hæmatin and eosin, hæmatin and Van Gieson, hæmatin and Sudan IV, Unna-Pappenheim, Verhoeff's elastic tissue stain, Gram, and Levaditi's method for spirochætes was also employed for the aorta.

Left Ventricle.—The muscle fibres showed marked cloudy swelling and there was considerable oedema between the muscle bundles. There was no evidence of interstitial change beyond a definite periadventitial fibrosis of the smaller arterioles. There was slight chronic

CONGENITAL SYPHILITIC MESAORTITIS

thickening of the fibrous pericardium, and there was marked hyperæmia of the epicardial capillaries. A large superficial branch of the left coronary artery showed no pathological change.

First Part of Aorta.—The adventitia showed well-marked fibrosis which was specially evident towards the junction of adventitia and media. The reflection of the visceral pericardium over the adventitia was clearly demonstrated, and the serosal cells appeared normal. Numerous vessels were present, including large branches of the vasa vasorum, which showed gross periadventitial



FIG. 3.—Adventitia of aorta showing periarteritis and endarteritis of vasa vasorum. $\times 60$.

fibrosis and some endarteritis (Fig. 3), and around many of the smaller vessels in the deeper layers of the adventitia were collections of lymphocytes and occasional plasma cells. No giant cells were seen. An external elastic lamina was fairly well defined in some places, but in others it was replaced by mature collagenous fibrils, poor in nuclei, which were being invaded by branches of the vasa vasorum. The latter encroached well into the media in places. For the most part the media was slightly thickened and showed smooth muscle associated with a definite increase in fibrous tissue. In Verhoeff preparations a marked quantitative diminution of elastic tissue

became evident, but for the most part the fibrils did not appear to be destroyed or interrupted. Here and there, however, were isolated fibrous scars, marking areas of complete destruction of the musculo-elastic tissue (Fig. 4). These scars centered round small branches of the vasa vasorum, and in places there was definite perivascular cuffing of the latter with lymphocytes. In one area the media was somewhat diminished in thickness and here the destruction of musculo-elastic tissue and replacement fibrosis was maximal. Corresponding to this area the intima was raised up into a plateau-like formation

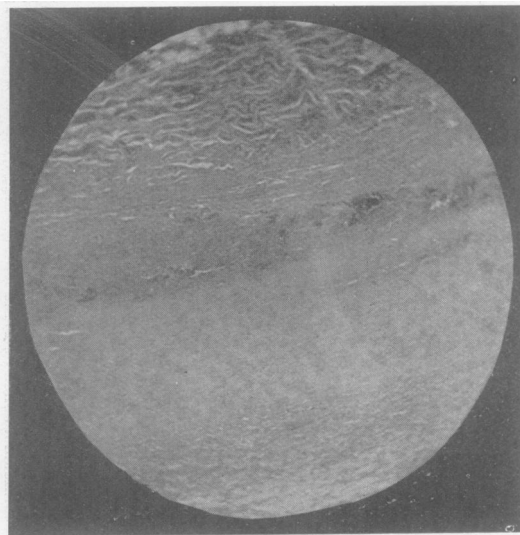


FIG. 4.—Aorta showing fibrous thickening of adventitia, vascular scars in media, and structureless intimal plaque. $\times 55$.

(Fig. 5). In relation to the less affected portions of the media the endothelial lining of the intima was represented by occasional flattened cells resting on a well-formed internal elastic lamina. The subintimal connective tissue, however, showed a slight preponderance of collagen over the elastic network. At the commencement of the above-mentioned intimal plateau, the subintimal connective tissue began to thicken and showed a structure of spindle cells lying in a network of fine fibrils split off from the internal elastic lamina. Towards the summit of the plateau the small amount of elastic tissue which remained was completely fragmented, and in places the collagen

CONGENITAL SYPHILITIC MESAORTITIS

fibrils were replaced by structureless necrotic tissue. Neither fat, cholesterin crystals, nor calcium salts were demonstrated. No spirochætes were demonstrated in Levaditi preparations.

A second portion of aorta taken from the region immediately above where the macroscopic lesions ceased showed nothing abnormal save a definite increase in fibrous tissue, associated with a few isolated scars in the media. There were no cellular collections.

Pulmonary Artery.—Beyond some medial fibrosis with

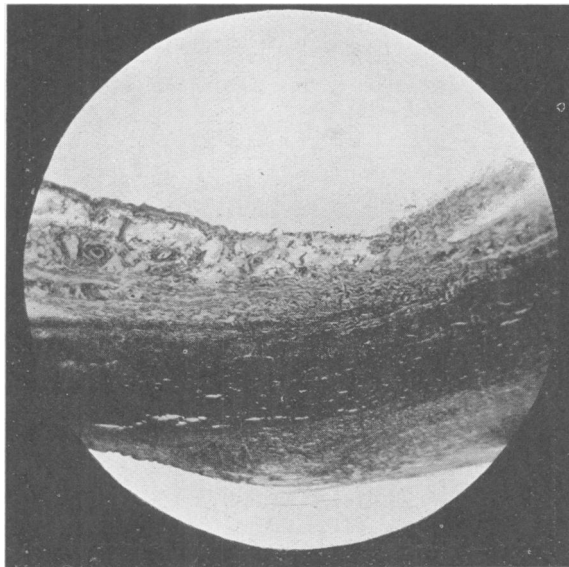


FIG. 5.—Aorta (Verhoeff's method). Showing destruction of elastic tissue, and intimal plaque. $\times 15$.

a suggestion of localised scarring nothing abnormal was found.

Superior Mesenteric Artery.—There appeared to be some periadventitial fibrosis, but media and intima were healthy.

Right Lung—Base and Root.—In the portion from the base there was no evidence of pleurisy or pneumonia, but intense terminal congestion and œdema were found. In places there had been extensive hæmorrhage within groups of alveoli; these areas were surrounded by zones of emphysema. There was no hyperplasia of the interstitial connective tissue of the lung. In the portion from the root the lung tissue showed similar appearances.

BRITISH JOURNAL OF VENEREAL DISEASES

A large branch of the pulmonary artery which was present showed nothing abnormal save slight periadventitial fibrosis. An associated lymph node showed anthracosis and intense congestion. There was reticulo-endothelial hyperplasia in the germ centres; some of the cells appeared necrotic and were separated from each other by inflammatory oedema. The lymph sinuses were distended and contained numerous mononuclear macrophages and a few polymorphs, associated with fibrinous *débris*. There

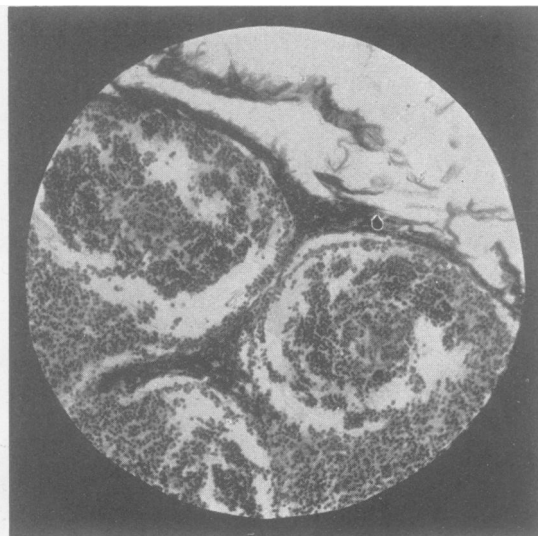


FIG. 6.—Mesenteric lymph node showing hyperplastic changes in germ centres of cortical nodules. $\times 100$.

appeared to be a generalised increase in the fibrous stroma of the node.

Lymph Nodes from Mesentery and Portal Fissure, and Spleen.—These showed intense congestion and changes in the germ centres similar to those described above (Fig. 6). No micro-organisms were demonstrated in the spleen.

Thymus.—Changes comparable to those seen in the other lymphoid tissue were present; congestion and hyperplasia of reticulum cells being marked, with evidence of necrosis in latter cells.

Liver.—A large amount of fat was demonstrated in the Sudan IV preparations. Some of the cells contained a single large globule and others several smaller discrete

CONGENITAL SYPHILITIC MESAORTITIS

globules. The normal architecture was so distorted that it was impossible to determine with accuracy the exact disposition of the fat, but the change appeared to be more intense towards the peripheral portion of the lobules. Those cells which were free from fat showed necrotic changes in nucleus and cytoplasm. In places the liver cells had entirely disappeared, being replaced by dilated sinusoids filled with red blood corpuscles. Bile-ducts were present in great excess over the normal, due to the loss of liver substance; their cells showed only slight

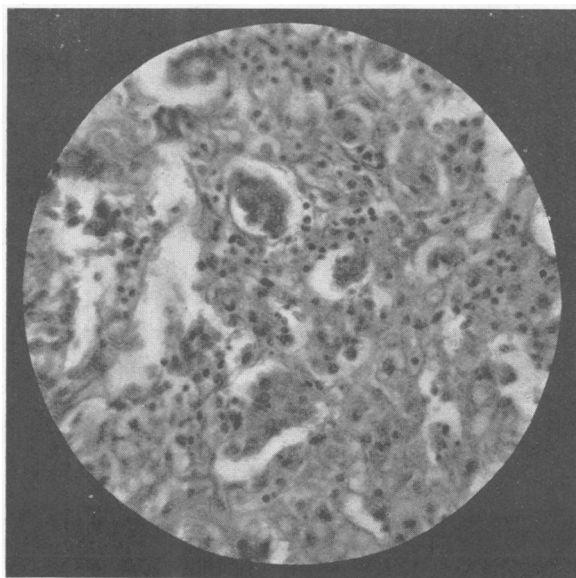


FIG. 7.—Liver showing necrotic and fatty changes in parenchymal cells, excess of bile-ducts, and infiltration with inflammatory cells. $\times 300$.

degenerative changes (Fig. 7). A definite interstitial hepatitis was present, there being focal collections of polymorphs, lymphocytes and mononuclear macrophages round the portal tracts, and similar cells were scattered more diffusely throughout the tissue. There appeared to be a definite peri-portal fibrosis, the larger bile-ducts being surrounded by dense scar tissue (Fig. 8). There was also collagenous thickening of the walls of the main branches of the portal vein. No micro-organisms were demonstrated in the liver.

Left Kidney.—For the most part the glomeruli showed

BRITISH JOURNAL OF VENEREAL DISEASES

intense congestion with escape of occasional red cells into Bowman's capsule, which in some cases also contained *débris* regurgitated from the tubules. There was some proliferation of endothelial cells in the glomerular tuft. The tubules showed intense cloudy swelling with fatty change in the convoluted portions, and in many places contained desquamated epithelial *débris*. There was no cellular infiltration in the interstitial tissue, but in several places fibrous scars were associated with completely hyaline glomeruli. The main branches of the

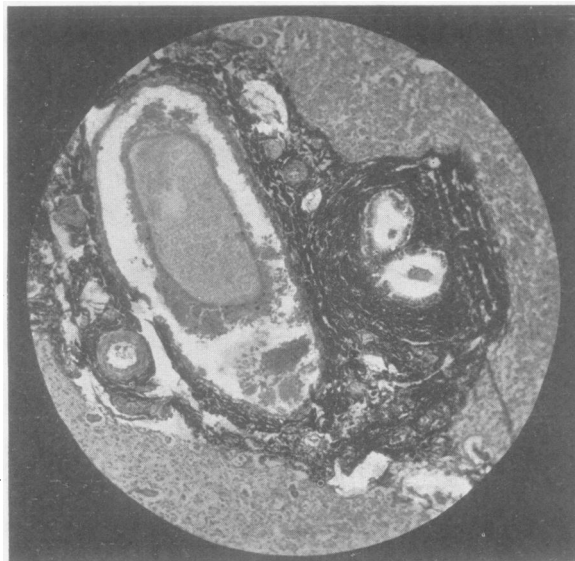


FIG. 8.—Portal tract showing scar tissue surrounding bile-ducts. $\times 75$.

renal artery appeared to be normal, save for some periadventitial fibrosis.

The stomach, pancreas, right testis and epididymis showed only changes attributable to intense toxæmia. In addition to such changes there was evidence of fibrosis (? post-inflammatory scarring) in the medulla of the *left suprarenal*. *The upper epiphysis of the right fibula* showed nothing abnormal.

DISCUSSION

The interest of this case lies in the presence of (a) congenital mesaortitis, and (b) acute liver necrosis, and

CONGENITAL SYPHILITIC MESAORTITIS

it will be found convenient to accord these conditions a separate discussion.

Whereas the observations of Warthin (1914, 1916, 1918) on congenital syphilitic myocarditis are well known, less attention has been paid to the fairly extensive literature on congenital syphilitic aortitis.

The pathology of the latter condition definitely resolves itself into a study of two distinct age groups: (1) foetal and infantile cases, (2) cases occurring in lues tarda.

It is interesting to note that while Döhle (1885) and Heller (1899) clearly established the relationship between acquired syphilis and aortic disease, Hennig (1890) and Mracěk (1893) described lesions suggestive of inflammatory change in the aortæ of infants dead of congenital syphilis.

Wiesner (1905) described morbid changes in the aortæ of 9 out of a series of 10 congenital syphilitic infants. The changes were limited to the media for the most part and consisted of an infiltration with inflammatory cells; perivascular cuffing of the vasa vasorum was noted. While these changes were characteristic in the new-born, in those cases which survived the picture was further modified by connective tissue hyperplasia and endarteritis of the vasa vasorum. In a three-months-old child cellular infiltration had almost completely disappeared, the appearances being those of healing by scar tissue and destruction of musculo-elastic elements. Haselbach (1905) also described inflammatory lesions in the aortæ of congenital syphilitics, and Bruhns (1906) confirmed Wiesner's work, but found changes in the adventitia also, thus bringing the histology more into line with that of acquired mesaortitis. Frohwein (1906) described the presence of *Treponema pallidum* in the aortæ of congenital syphilitic infants, and Wiesner and Rach (1907) demonstrated the causal organism in 4 out of 16 cases of infantile mesaortitis. Spirochætes have also been described in such cases by Sabrazès and Dupériér (1909), Cesa-Bianchi (1915), and others, but Stolkind (1920), in reviewing the literature, failed to find evidence of detection of *Treponema pallidum* in the aortæ of congenital syphilitics of more than a year old. Waterman (1908) confirmed the histological findings in infantile mesaortitis and suggested that aneurysm might be a late result. Klotz (1908) described aortic lesions in a stillborn child.

which histologically were acute. He suggests that the healed lesions of congenital syphilis may give rise to a mistaken diagnosis of acquired syphilitic aortitis in the adult. Debove and Tremolières (1910) also described specific morbid changes in the aortæ of infants, and Rebaudi (1912) and Levy-Franckel (1912) each published a series of cases which further confirmed congenital syphilitic aortitis as a pathological entity. Etienne (1920) goes so far as to say that 50 per cent. of new-born syphilitics show aortic lesions. Both Thoenes (1922) and Ziedler (1922), in addition to describing adventitial and medial changes in the aorta, drew attention to the presence of connective tissue hyperplasia in the intima.

A survey of the literature thus suggests that the presence of specific lesions in the aortæ of congenital syphilitic infants is by no means a pathological rarity, but the figures given by Matusoff and White (1927) offer somewhat conflicting evidence. In 3,300 autopsies on children, 35 cases which showed anatomical evidence of congenital syphilis were found; and in only 3 of these were lesions demonstrated in the aorta (the age of these cases is not stated).

As regards the gross anatomy of foetal and infantile congenital mesaortitis I can find no records in the literature of any definite and specific appearances.

The morbid histology of the condition may be summarised as follows:—

(1) Initial invasion of the adventitia and media by lymphocytes, plasma cells and occasional giant cells, associated with the presence of *Treponema pallidum*.

(2) Perivascular cuffing and endarteritis of vasa vasorum, and deep invasion of media by latter.

(3) Destruction of musculo-elastic tissue of media followed by healing by scar tissue.

(4) Resulting connective tissue hyperplasia of intima, with thickening of the latter.

(5) Development of necrosis in thickened intima.

Notwithstanding the resemblance of these lesions to the appearances found in acquired mesaortitis, and the fact that the causative organism has been demonstrated in association with them, their specificity has been denied by several observers. Amongst these are Thorel (1910), Chiari (1928), and Siegmund (1929), who state that rheumatic infection of the aorta can simulate the lesions

CONGENITAL SYPHILITIC MESAORTITIS

of syphilis. Scharpf (1909) contests Wiesner's findings on the grounds that the cellular aggregations may be found physiologically in normal aortæ. Wiesner (1910) states that while such may be the case in longitudinal or tangential sections through the vasa vasorum in normal aortæ, the variety of inflammatory cells which he has described as specific of syphilis is not displayed. Trachtenberg confirmed Wiesner's findings in this respect, and it seems unlikely that the specificity of the lesions can be disproved.

While most observers are agreed that the lesions take the form of a mesaortitis spread through the vasa vasorum, Winternitz (1913) describes huge collections of spirochætes in the intima of the aorta in congenital syphilis, and the view that infection takes place from the intima inwards as well as through the vasa vasorum is further championed by McMeans (1930) in the case of acquired syphilis.

The literature on aortitis as a manifestation of lues tarda is very scanty with regard to morbid anatomy. Turnbull (1911) described a case of syphilitic mesaortitis with aortic incompetence in a female aged seventeen, whose father also suffered from a similar condition, and a case of mesaortitis in a male aged seven. In both cases the gross and microscopic appearances were characteristic and resembled the lesions of acquired syphilis, but no spirochætes were demonstrated. Von Zetkowsky (1916) described typical mesaortitis, stenosis of coronary arteries, aneurysm of descending thoracic aorta and aortic incompetence in a female aged seventeen, who had been treated for congenital syphilis as a child. Paul (1923) quotes a case of mesaortitis with aneurysms of thoracic and abdominal aorta (the latter ruptured), in a female aged eighteen. The father had a positive Wassermann reaction. Nixon (1911) describes an aneurysm of the abdominal aorta which was regarded as being of syphilitic origin in a female aged twenty, with Hutchinson's teeth. Wilson and Marcy (1907) cite a case of aortitis with a ruptured thoracic aneurysm in a child of four years. The evidence in favour of syphilis is inconclusive in this case. Schulte (1930) describes typical mesaortitis in a male aged thirteen. The specimen was an old one dating from 1884 and no family history was available. This observer gives an excellent review of the literature on the

subject. Martland (1930) quotes figures which bear out the rarity of this condition so far as autopsy records go. In 300 cases of death due to heart disease, 101 were found to be due to syphilis of the aorta and heart. Congenital mesaortitis was only found in one case, that of a male negro aged ten, who exhibited other signs of congenital lues.

My own case falls definitely into the group under discussion. The aortic lesions represent an apparently healed condition, but in view of the amount of vascularisation and cellular infiltration present, it is doubtful whether the lesions can be regarded as being completely obsolete.

The age of the patient, family history, Wassermann reaction and presence of interstitial keratitis afford corroborative evidence that a diagnosis of juvenile syphilitic mesaortitis is correct.

In contrast to the sparse anatomical records of aortitis in lues tarda the frequency with which a clinical diagnosis is made is very striking. References to a diagnosis of the condition made by the history and clinical examination alone are found in communications by Huchard (1899), Marchand (1907) and Chiray and Ségard (1908), but these cases must be regarded as being extremely doubtful. Bierman (1911) described a case in a male of nineteen with a positive Wassermann reaction and definite X-ray findings. There was improvement of the aortic condition under specific treatment. Cases are recorded by Stadler (1912) and by Fournier (1912) in whose case, though the patient was apparently a congenital syphilitic, a diagnosis of aortitis was not made till the age of forty. Lippman (1913) quoted a case of aortic regurgitation in a male of seventeen (with a positive Wassermann reaction), which he regards as being due to congenital syphilis. Neugebauer (1914) records aortic incompetence associated with a positive Wassermann reaction in three sisters aged thirty-two, twenty-eight and seventeen. The mother died of apoplexy at the age of forty-three, and had had three abortions, and a seventeen-year-old brother died suddenly during a heart attack. Veeder and Jeans (1914) quoted 123 cases of manifest congenital syphilis, 60 per cent. of which occurred in older children, and found one case of aortitis (no details), and Stoll (1914) in a familial study of congenital syphilis found evidence of aortic disease in several children whose parents suffered from

CONGENITAL SYPHILITIC MESAORTITIS

latent syphilis. Heiman (1919) described an aneurysm of the aortic arch in a male of thirteen with a positive Wassermann reaction. Definite clinical and X-ray signs were present.

The brothers Bretervide (1924) described experiments wherein the aortic systems of children's cadavers having been injected with bismuth paste, teleroentographic examination was carried out. It is stated that in infants up to the age of eight the origins of both aorta and pulmonary artery are found to the left of the mid-sternal line, which overlaps the left border of the ascending aorta. Thus in children up to this age diastolic reinforcement in the pulmonary area is really aortic in origin. These observers believe that the widespread incidence of congenital syphilis and its localisation in the aorta are responsible for an accentuated aortic second sound, and that this sound is commonly regarded as emanating from the pulmonary artery (normal accentuation of second pulmonary sound in children). They stated (1925) that a controlled orthodiagraphic study of the aorta in 463 congenital syphilitic children indicated that whereas the normal diameter of the ascending aorta is 1 cm. up till eight years of age, and 1.3 cm. between eight and fourteen years, it is wider and the shadow more opaque in congenital syphilitics. Hence they regard X-ray findings of the greatest importance in the diagnosis of congenital mesaortitis. Hausman (1925) described 5 cases of congenital mesaortitis amongst which were aortic insufficiency in a male of seven (Wassermann reaction +++ father syphilitic), and aortic dilatation and incompetence in a virgin of thirty-eight. She had a strongly positive Wassermann reaction and anginal symptoms. Her father and three sisters had died suddenly from heart disease.

Gesteira (1927) emphasised the importance of an accentuated aortic second sound, without hypertension and without other stethoscopic signs, in the diagnosis of congenital mesaortitis. He studied a series of nine children between eight and thirteen years old. All had a positive Wassermann reaction, an accentuated aortic second sound and according to the Bretervides' technique had positive X-ray findings in the aorta. Specific treatment caused improvement in every case. He draws attention to the rarity (*sic*) of aortic lesions in childhood other than those

CONGENITAL SYPHILITIC MESAORTITIS

due to syphilis and contends that congenital mesaortitis is more frequent than hitherto imagined, but is often missed due to its early modification by treatment. Reiche (1926) described anginal symptoms and aortitis with aortic incompetence in a male of twenty-five with a tabetic mother and Schlesinger (1928) quotes two cases of aortitis with aortic incompetence in young adults, which he regards as being due to congenital mesaortitis. Locatelli (1929) described mesaortitis in three brothers aged thirty, twenty-seven and twenty-three. The eldest died, but the two younger patients who suffered from angina pectoris, nausea, retro-sternal pain, etc., improved visibly under appropriate treatment.

Kurtz, Eyster and Madison (1930) studied 12 cases of congenital syphilis. The series included four males and eight females, the ages ranging from nine to thirty-three years, with an average of nineteen years. Seven had had no antiluetic treatment, and the remainder had been treated for three or four years before examination. The methods employed included clinical history, physical examination, Wassermann reaction, orthodiagraphy and electrocardiography. Of the four males, three showed signs of aortitis and one none. Six of the females showed no such signs and two showed slight signs. Hence in 41·6 per cent. of the cases there was evidence of a slight or moderate degree of aortitis.

A study of the literature thus shows that a clinical diagnosis of mesaortitis in lues tarda has been made with increasing confidence during the last thirty years, such a diagnosis having been materially aided by the employment of methods which were not available to the older observers. The evidence on which the diagnosis has been made may be briefly summarised as follows:—

(1) Clinical history with special reference to family history.

(2) Clinical history and physical examination of parents.

(3) The existence of a symptom complex in patient consisting of angina pectoris, retro-sternal pain, predisposition to fatigue, etc.

(4) Physical examination of the patient with special reference to (a) manifestations of lues tarda such as keratitis, Hutchinson's teeth, etc. ; (b) signs of an aortic lesion, especially an accentuated aortic second sound.

BRITISH JOURNAL OF VENEREAL DISEASES

- (5) Positive Wassermann reaction.
- (6) Positive orthodiagraphic findings.
- (7) Certain abnormal electrocardiographic findings.
- (8) Alleviation of aortic symptoms after specific treatment.

Whereas positive findings in a due proportion of the above leave no doubt as to the diagnosis among numerous observers, a considerable weight of evidence is available that such a diagnosis cannot be made with certainty. Stolkind (1920) stated that up to that date he had been unable to find in the literature a single proved case in older children, adolescents and adults. He draws attention to the fact that the existence of a positive Wassermann reaction is not proof that an aortic lesion is of syphilitic origin, and that rheumatic infection in a congenital syphilitic may give rise to confusion. He further notes that Hutchinson's teeth have been described in non-syphilitic children and that their presence cannot be cited as evidence of the specificity of an aortic lesion. Attention is also drawn to the possibility of an extra-genital primary infection in infancy. This observer quotes two cases of proved congenital syphilis in whom signs of aortic disease were evident during life, but at autopsy no evidence of syphilitic aortic disease was found.

Matusoff and White (1927) in a study of 25 cases of congenital syphilis (orthodiagraphy employed in 8 cases) failed to find evidence of involvement of heart and aorta, and state that the presence of indefinite signs is suspicious of rheumatic infection. Previtali, Nicholson and Moon Adams (1930) investigated 22 male and 28 female congenital syphilitics, all of whom had a ++++ Wassermann reaction on admission. Orthodiagraphy and electrocardiagraphy were employed in the physical examination. No evidence of involvement of the aorta was found. Givan (1930) found no definite evidence of aortic involvement in a series of 417 congenital syphilitics. McCullough (1930), in a review of 939 cases of congenital syphilis occurring among 40,750 admissions under the age of fifteen, found no evidence to suggest that syphilis contributes to cardio-vascular disease up to this age.

It now remains to consider these divergent views in the light of the pathology of congenital mesaortitis. As regards the infantile manifestations, the absence of gross anatomical lesions in the aorta precludes the possibility

CONGENITAL SYPHILITIC MESAORTITIS

of definite physical signs, and functional disability (if any) is likely to be merged in the general symptomatology of the condition. Hence a clinical diagnosis at this stage must be a virtual impossibility.

The question of the actual time when the causative organism produces its specific effects in the aorta is a controversial matter. According to Veeder and Jeans (1924), infection takes place late in pregnancy, since 37 per cent. of congenital syphilitics give a negative Wassermann reaction at birth. This view is supported by Herxheimer (1928), who believes that only towards the end of pregnancy does the foetus exhibit allergic properties towards the presence of spirochætes. At an earlier stage in foetal life tissue reactions are absent. Hence the cellular infiltrates may be regarded as the first signs of reaction. Connective tissue hyperplasia and endarteritis obliterans come later, and may be regarded as the final defence mechanism. The sequelæ of these early stages must depend on (a) the virulence of the infection and the resistance of the individual, (b) the effect of intra-aortic pressure on a weakened vessel, (c) the recrudescence and aggravation of existing lesions in the aorta which may occur with other manifestations in *lues tarda*, (d) the effect of treatment.

It seems likely from the scanty anatomical records of the condition in older children, adolescents, and adults, compared with the proved high incidence of aortic infection in infancy, that spontaneous recovery is very common, and *that healing is complete at a comparatively early age*. Taking this in conjunction with the fact that clinical investigation in this particular disease is open to many fallacies, I have difficulty in accepting the view that an absolute clinical diagnosis can be made with the certainty claimed by numerous observers. In the case which I have described it seems inconceivable that orthodiagraphy could have revealed anything abnormal in the aorta, and symptoms or signs of aortic disease were not present during life, as might be expected from the autopsy findings. It would appear, however, that in some individuals the infection is so virulent that maximal damage to the aorta is done, and in such cases the late results become indistinguishable from the lesions found in acquired mesaortitis. Thus in the cases described by Turnbull a clinical diagnosis of aortitis with aortic

BRITISH JOURNAL OF VENEREAL DISEASES

incompetence was made, and corresponding lesions were found at autopsy. In Schulte's case, though the aortic valve was unaffected, the gross changes in the aorta appear likely to have given positive X-ray findings, had such methods been available. In a few recorded cases progressive weakening of the aortic wall has led to aneurysm formation (Von Zetkowsky, Paul). An absolute clinical diagnosis in these severe cases ought therefore to be possible, but they appear to be extraordinarily scanty. Moreover, in dealing with adult cases the possibility of primary acquired genital or extragenital infection must be carefully excluded before making even an anatomical diagnosis of congenital mesaortitis. We have in the museum of this Department a specimen of syphilitic aortitis and aortic endocarditis with stenosis of the coronary orifices taken from a prostitute aged twenty. She had a definite history of a primary genital infection of comparatively recent date.

In conclusion it may be stated that whereas congenital mesaortitis is probably more widespread than is generally supposed the degree of healing is usually so complete that the condition is of minimal importance compared with other visceral manifestations of congenital syphilis. It would appear that definite clinical recognition of the condition is only possible in a few cases.

In discussing my case as an example of acute liver necrosis it is of importance to note that two of the factors which have been from time to time held responsible for the condition were present, *e.g.*, syphilis and arsenic. The patient was under treatment for fifty-seven days, during which time he received five 0.15 gm. doses of novarsenobillon at intervals averaging eleven days. No untoward symptoms were noted till seventeen days after the last injection had been given. Thereafter the final illness presented the usual manifestations of acute liver necrosis. This diagnosis was confirmed at autopsy, the appearances in the liver suggesting that the condition had been present for some days, and was not an example of the fulminant type of case where there is a pure "red necrosis" of the liver without fatty metamorphosis. Apart from the usual toxic changes seen in the organs, a striking feature was reticulo-endothelial hyperplasia in the lymphoid tissue of the body, with necrosis of the hyperplastic cells.

CONGENITAL SYPHILITIC MESAORTITIS

It seems impossible to defend the theory that acute liver necrosis is caused by any one specific factor. Numerous cases of the condition arising in untreated acquired syphilis have been cited. The possibility of its occurrence in congenital syphilis also seems likely. A case of atrophic coarse cirrhosis of the liver in a female congenital syphilitic imbecile aged thirty-five is reported by Paddle '1932'. She had been under institutional observation since the age of eight, and alcohol could be excluded as a causative factor. Jaundice was first noted thirty months before death, and increase in the size of the liver and spleen were progressive. The Wassermann reaction was strongly positive. It was considered that the condition might have arisen (*a*) as a sequel to an attack of scarlet fever two years before symptoms developed, or (*b*) consequent on congenital syphilitic cirrhosis of the liver. At autopsy atrophic cirrhosis of the liver, splenomegaly with cirrhosis, and multiple infarction of the lungs were found, and were confirmed by histological examination. No spirochætes could be demonstrated in liver or spleen. Through the courtesy of Dr. Paddle I have had an opportunity of examining sections of liver and spleen from this case, and of ascertaining that the patient had no arsenical treatment at any time, and that there was no history of a febrile attack when the jaundice commenced. From a study of the liver I have formed the impression that in addition to the appearances diagnostic of atrophic cirrhosis, certain features also exist which are not commonly seen in typical examples of this condition. These may be summarised as (1) very irregular distribution of unduly broad bands of connective tissue, (2) an excessive number of vessels and bile-ducts in the latter, (3) the occurrence of focal areas of round cells suggesting interstitial hepatitis. It is therefore possible that the condition may be one of multiple nodular hyperplasia, the late stage of subacute liver necrosis. The distinction between this condition and atrophic cirrhosis is notoriously difficult.

The numerous cases of acute liver necrosis which occurred during the War emphasised the importance of arsenic as a causative factor, and although the proportion of fatal cases of the disease during salvarsan treatment is very small in comparison with the widespread use of the drug, yet the not uncommon cases which during treatment

display slight signs and symptoms of hepatic damage lend credence to the theory.

Finally, in consideration of the numerous cases of the disease which have arisen in the absence of either syphilis or arsenic, *i.e.*, post-infective, puerperal, and the so-called cryptogenic cases, it seems clear that the liver damage depends on (a) predisposing, (b) precipitating and possibly (c) terminal factors, and not on any one causative agent.

The susceptibility of the liver to bacterial and metabolic toxins is well demonstrated in the case of syphilis, where permanent damage may be assessed by clinical and autopsy investigations, but there must be numerous conditions causing liver damage which the body can withstand in the absence of further hepatic insults. With regard to the *rôle* of organic arsenicals as a precipitating factor the general belief is that the benzol fraction may be excluded. Strathy, Smith and Hannah (1920), in a study of fifty-nine syphilitics under salvarsan treatment who showed liver symptoms, regarded the condition as being typical of delayed arsenical poisoning, and contend that neither age, sex, nor preparation or composition of the drug are causative factors.

As to the actual mechanism of the action of arsenic, studies on the fatty changes in the liver and kidneys in fatal post-salvarsan cases, and the fact that experimentally those tissues which have the highest fat content contain the greatest quantity of arsenic, have given rise to the theory that arsenic in some way combines with the food fat, and is carried to the liver.

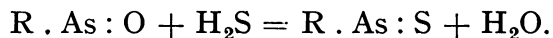
Foulerton (1920) pointed out that the fatty changes in the liver and kidneys of fatal cases are essentially similar to those found in poisoning with chloroform and tetrachlorethane (fat solvents) and in dinitrobenzene, trinitrotoluene and phosphorus poisoning (readily soluble in fat). In acute yellow atrophy the food fat combined with arsenic is carried to the liver where interstitial hepatitis and toxic effects on the liver parenchyma render the liver cells unable to metabolise the fat, with consequent engorgement with food fat. A lipæmia and engorgement of the kidneys with unchanged food fat then ensues. Foulerton was of the opinion that the benzol fraction materially adds to the toxicity of the drug. In a later paper (1921) he emphasised the fact that the rapid and

CONGENITAL SYPHILITIC MESAORTITIS

massive fatty metamorphosis in the liver cannot be a result of an intrinsic fatty degeneration of the liver cells. In considering the cases where symptoms do not ensue till many weeks after the administration of the drug had ceased, he believed that during treatment insufficient poison is concentrated in the liver to manifest itself by immediate jaundice. Accumulation goes on in the fat depots, and hence when a variation in the nutrition of the patient ensues, *e.g.*, the sudden mobilisation of reserve fat which may take place when a soldier goes back to full duty after weeks of a hospital *régime*, the liver may be flooded with arsenic-containing fat. In this way the apparent discrepancies between the time and amount of drug factors and the onset of symptoms is explained. Indirect evidence in support of this theory is obtained from the work of Duret (1918), who studied the excretion of arsenic in men under antisypilitic treatment. It was found that the maximum amount of arsenic which the kidney could excrete in twenty-four hours was 0.1 gm., and having allowed for the amounts excreted in skin and fæces, an unaccounted for fraction remained which must have undergone temporary fixation in the tissues. Excretion of arsenic was still going on twenty days after the last dose had been administered.

However, grave objections to Foulerton's theories may be advanced. He admitted himself that there is no evidence available which proves that arsenic has a chemical affinity towards fat, and the fulminant cases of "red necrosis" without fatty change suggest that the arsenic may damage the liver by some other means than fixation in food fat.

An alternative theory of the action of arsenic is afforded by the researches of Voegtlin, Dyer and Leonard (1925), who adduce certain experimental evidence that the action of arsenic on mammalian protoplasm depends on its effect on certain organic sulphur compounds containing sulphur in the sulphydril form. It can be shown *in vitro* that arsenious oxide and its organic derivatives combine with H_2S or certain SH compounds according to the equation :



It is known that all protoplasm with an active metabolism contains SH compounds. Arsenic in the form of 3 amino

4 hydroxyphenyl-arsenious oxide was administered to rats, and it was found that a previous intravenous injection of either reduced glutathione or cysteine had a detoxicating effect, as evidenced by longer survival than in control animals. Both these compounds contain the SH group. It was found that glutathione was the more efficacious of the two, and manifested its protective action even when given twenty minutes after the arsenic. In addition it was shown that the addition of glutamic acid and cysteine to the diet reduced the toxic effect of the arsenic. Hence indirect evidence is given that glutathione is synthesised in the tissues from these amino acids. This is put forward as a more likely explanation than that glutathione is contained in the food and escapes hydrolytic cleavage during digestion, or is found as the result of breaking down of tissue proteins. Since this work was published Hopkins (1929) has shown that glutathione is a tripeptide composed of glycine, glutamic acid and cysteine, and not a simple dipeptide of glutamic acid and cysteine as previously apparently established by himself. A pure crystalline thiol compound has been prepared from yeast and from red blood cells by this observer, and the percentage analysis corresponds with the composition of a tripeptide containing the above three amino acids.

This work, however, does not necessarily invalidate the final conclusion of Voegtlin *et al.* that "it is indicated beyond doubt that arsenic in the form of the trivalent directly toxic oxide exerts its action on mammalian protoplasm through its chemical affinity to the SH group of reduced glutathione, thus interfering with the normal equilibrium between oxidised and reduced glutathione as a result of which the tissue dies of asphyxia."

Craven (1931) casts doubt on the evidence on which a high carbohydrate and low fat diet is recommended during arsenical treatment, this being a natural outcome of the theory that arsenic is fixed in fat. Though the changes in the liver in chloroform and arsenic poisoning may resemble each other, he is unable to reconcile the chemical dissimilarity between drugs such as arsphenamin and chloroform, with a suggestion that a low fat diet is a prophylactic indication during arsenical medication. In a series of thirty dogs, ten each were placed on high carbohydrate, fat and protein diets. Arsphenamin was

CONGENITAL SYPHILITIC MESAORTITIS

administered in exactly equal amounts based on the body weights of the animals. The onset of liver damage was estimated by serial Van den Bergh reactions, and its amount was assessed by killing the animal followed by histological examination of the liver. It was shown that whereas high fat and high protein diets afforded the maximum protection against liver injury from arsphenamin; high carbohydrate diets afforded the maximum susceptibility. Starvation was found to be an important predisposing factor to liver injury. The administration of cysteine failed to produce a detoxicating effect.

No matter in what way arsenic acts as a precipitating factor in the production of acute liver necrosis, I am strongly of opinion that previous liver damage must be presumed. That the condition may not arise *de novo* and depends on the action of some special virus on a previously damaged liver was pointed out by McDonald (1908), and again when he reported (1918) a series of five cases of acute yellow atrophy occurring in syphilitics in the course of or subsequent to treatment with salvarsan preparations and mercury. At autopsy cultures from the heart blood and lung in these cases gave a copious growth of organisms of the coli-typhoid group which in two out of three strains tested gave some definite cultural characteristic features and pathogenic properties. McDonald admitted that livers previously damaged by syphilis and possibly arsenic *plus* mercury might naturally be expected to have suffered considerable loss in their local protective mechanism, *i.e.*, Kupffer cells, the way being thus paved to an absolutely terminal invasion of the liver by micro-organisms from the alimentary tract. Thus post-mortem contamination, or even invasion of the blood *via* the liver in the last few hours of life might reasonably be anticipated in many of these cases; but McDonald was also of the opinion that such invasion might occur earlier and might actually be an essential factor in determining the final necrosis. No observations in the direction of demonstrating organisms in the circulating blood during life were made in these cases, so that more conclusive evidence in favour of this hypothesis is at present lacking.

McDonald's suggestion that microbic invasion may be a *terminal* factor in liver necrosis has been subjected to some misinterpretation by the Salvarsan Committee of the Medical Research Council (1922), who appear to have

BRITISH JOURNAL OF VENEREAL DISEASES

considered that this observer wished to make out a *prima facie* case for microbic invasion as the *essential* factor, without consideration of primary damage to the liver by other agencies, a contention which is not supported on reference to the original paper in 1918. However, in the final conclusions of the Committee as to the rôle of salvarsan in the ætiology of acute liver necrosis, a suggestion is made that the poisonous action of salvarsan compounds may be dependent "on the presence of adjuvant circumstances as yet unknown."

Ruge (1932) in a study of 2,500 cases of jaundice carried out over a period of ten years is of the opinion that simple jaundice and post-salvarsan jaundice are the same disease, the causal factor being bacteria related to the coli-typhoid group. He is of opinion that the predominance of jaundice in salvarsan-treated syphilitic men is explained by previous damage to the liver by syphilis and salvarsan. Willcox (1931) also draws attention to hypohepatism and necrosis of the liver in catarrhal jaundice and states that "there is no variety of toxic jaundice produced from chemical exogenous poisons for which an exact counterpart may not occur from biological toxins, and the converse is also true." Findlay and Dunlop (1932) report a fatal case of acute necrosis of the liver associated with epidemic catarrhal jaundice, and consider the latter condition to be caused by a virus infection. These observers hold that the precipitation of acute liver necrosis depends on superadded toxæmia in a patient whose liver has not fully recovered from the primary attack of the virus, and stress the importance of recognising that the combination of a toxin and infection produce more widespread liver necrosis than the action of either agent alone.

It is interesting to note that in my own case, though I was unable to demonstrate organisms in liver or spleen by direct methods, the widespread reticulo-endothelial hyperplasia in the lymphoid tissue is more suggestive of reaction against organismal invasion than the results of a toxic process. It is not impossible that infection with a living virus may take place as a terminal phenomenon in acute liver necrosis, and the occurrence of limited outbreaks of the disease during and after the war lends some support to the theory.

In conclusion, the actual amount of arsenic admini-

CONGENITAL SYPHILITIC MESAORTITIS

stered in the case which I have described may be considered. The preparation of novarsenobillon employed contained 20 per cent. of arsenic. Hence each of the five 0.15 gm. doses of the drug contained 0.03 gm. of arsenic. If the figures given by Duret are correct, *i.e.*, the maximum excretion of arsenic in twenty-four hours by the kidney alone equalling 0.01 gm., then in my case, since an average of eleven days elapsed between the doses, the arsenic content of any one dose should have been entirely excreted before the next dose was given. It must be admitted, however, that the age of the patient may have modified the amount of arsenic excreted. There was nothing in this case to indicate clinically that renal function was in any way deranged, but the possibility of damage to the convoluted tubules during syphilitic spirochæturia which has been pointed out by Warthin (1922) cannot be discounted. However, even when taking these factors into account, it seems very unlikely that the fractional amount of arsenic administered could damage a healthy liver. It was difficult to assess any histological changes in the liver since the finer details were obscured by the necrosis, but definite periportal fibrosis was present, and there may well have been other permanent damage following on syphilitic cirrhosis present at birth. The seventeen-day latent period between the last injection and the appearance of symptoms suggests cumulative activity on the part of the drug causing necrosis of liver cells and possibly rendering them susceptible to terminal infection with a living virus.

In this case there were no signs or symptoms during treatment to indicate any untoward events in the liver. In the absence of Herxheimer reactions, loss of weight, etc., it seems a difficult matter to know when treatment should be discontinued. It would appear, therefore, that indications of hepatic damage can only be obtained through laboratory diagnosis. In view of the controversy surrounding special tests for hepatic function, it is suggested that performance of quantitative Van den Bergh reactions as a routine before the commencement of a course of arsenical treatment and at regular intervals during the course (if possible before each injection) would afford direct evidence of latent jaundice. In this way disasters might be avoided.

It seems clear that if the work of Craven on the dietetic

BRITISH JOURNAL OF VENEREAL DISEASES

prophylaxis of liver necrosis and that of Voegtlin *et al.* on the mode of action of arsenic on mammalian protoplasm receive confirmation, a field is opened up which may have an important bearing on the prophylaxis and treatment of acute liver necrosis.

SUMMARY

A case of acute liver necrosis in a congenital syphilitic aged nine undergoing arsenical treatment is described. The only definite evidences of syphilis disclosed by routine anatomical and histological investigation were interstitial keratitis and mesaortitis. The literature on congenital syphilitic mesaortitis is reviewed, and it is suggested that definite clinical recognition of the condition is very rarely possible.

The relationship between arsenic and liver damage is discussed, and it is held that acute liver necrosis only arises as the result of some toxic agent on a previously damaged liver.

Attention is drawn to certain recent investigations on the influence of diet during arsenical treatment and on the mode of action of arsenic on mammalian protoplasm.

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REFERENCES

- BIERMANN: *Deutsche. Med. Woch.*, 1911, 1157.
BRETERVIDE (Bros.): *Arch. d. Med. d. mal de l'enf.*, Paris, 1924, **XXVII.**, 257 (Ref. Gesteira).
BRETERVIDE (Bros.): *Archivos Lat. Amer. de Pediatría*, Buenos Aires, 1925, **19**, 797 (Ref. Gesteira).
BRUHNS: *Berlin Klin. Woch.*, 1906, **XLIII.**, 217 and 268 (Ref. Schulte).
CESA-BIANCHI: *Sifilide d. apparato cardio vascolare*, Milano, 1915 (Ref. Stolkind).
CHIARI: *Beit. path. anat.*, 1928, **80**, 336 (Ref. Schulte).
CHIRAY and SÉGARD: *Bull. et mem. soc. mem. Hôp. de Paris*, 1908, **XXVIII.**, 275 (Ref. Stolkind).
CRAVEN: *Bull. Johns Hopkins Hosp.*, 1931, **XLVIII.**, 131.
DEBOVE and TREMOLIÈRES: *J. Med. Franç.*, 1910, **IV.**, 158. (Ref. Stolkind).
DÖHLE: *Diss. Inaug.*, Kiel, 1885 (Ref. Schulte).
DURET: *Compt. rend. d. soc. d. Biol.*, 1918, **I.**, 31, 736.
ETIENNE: *La syphilis vasculaire. Congres Franc. de Medecin.*, 1920, (Ref. Schulte).

CONGENITAL SYPHILITIC MESAORTITIS

- FINDLAY and DUNLOP : *Brit. Med. Journ.*, 1932, April 9th, 652.
 FOULERTON : *Brit. Med. Journ.*, 1920, **I.**, 864.
 FOULERTON : *Journ. Path. and Bact.*, 1921, **XXIV.**, 3, 257.
 FOURNIER : *Syphilis héréditaire de l'âge adulte*, Paris, 1912 (Ref. Stolkind).
 FROHWEIN : *Med. Klinik*, 1906, **II.**, 439 (Ref. Stolkind).
 GESTEIRA : *Arch. d. Med. d. mal de l'enf.*, Paris, 1927, **XXX.**, 633.
 GIVAN : *Amer. Heart Journ.*, 1930, **6**, 132.
 HASSELBACH : *Diss. Griefswald*, 1905 (Ref. Stolkind).
 HAUSMANN : *Munch. Med. Woch.*, 1925, **72**, 2093.
 HEIMAN : *Arch. Pediat.*, 1919, **36**, 543 (Ref. Matusoff-White).
 HELLER : *Verh. Dtsch. path. Ges.*, 1899, 346.
 HENNIG : *Jahrb. f. Kinderheilk.*, 1890, **XXX.**, 106 (Ref. Stolkind).
 HERXHEIMER : *Verh. Dtsch. path. Ges.*, 1928, 144 (Ref. Schulte).
 HOPKINS : *J. Biol. Chem.*, 1929, **84**, 269.
 HUCHARD : *Maladies du Cœur et de L'aorte*, Paris, 1899-1905 (Ref. Stolkind).
 KLOTZ : *Journ. Path. and Bact.*, 1908, **XII.**, 11.
 KURTZ, EYSTER and MADISON : *Amer. Heart Journ.*, 1930, **6**, 67.
 LEVY-FRANCKEL : *Arch. d. mal. d. cœur*, 1912, **V.**, 625 (Ref. Stolkind).
 LIPPMAN : *Derm. Woch.*, 1913, **56**, 213.
 LOCATELLI : *Semana Med.*, 1929, **II.**, 1439 (Ref. *Zentralbl. f. Haut. u. Geschlechtskr.*, 1930, **XXXIII.**, 400).
 MCCULLOUGH : *Amer. Heart Journ.*, 1930, **6**, 132.
 McDONALD : *Edin. Med. Journ.*, 1908, **I.**, 83.
 McDONALD : *Brit. Med. Journ.*, 1918, **I.**, 76.
 MCMEANS : *Amer. Heart Journ.*, 1930, **6**, 43.
 MARCHAND : *Munch. Med. Woch.*, 1907, **LIV.**, 636 and 908 (Ref. Stolkind).
 MARTLAND : *Amer. Heart Journ.*, 1930, **6**, 1.
 MATUSOFF and WHITE : *Amer. Journ. Dis. Child.*, 1927, **XXXIV.**, 390.
 MEDICAL RESEARCH COUNCIL : *Reports of the Salvarsan Committee*, **2**, 1922, 85-86.
 MRACEK : *Arch. f. Dermat. u. Syph. Wien.*, 1893, **XXV.**, Ergänzt-Heft (Ref. Klotz).
 NEUGEBAUER : *Wien. Klin. Woch.*, 1914, 503.
 NIXON : *Journ. Barts. Hosp.*, 1911, **XLVII.**, 43.
 PADDLE : *Brit. Med. Journ.*, 1932, February 6th, 233.
 PADDLE : Personal communication.
 PAUL : *Virch. Archiv.*, 1923, **59**, 240.
 PREVITALI, NICHOLSON and MOON-ADAMS : *Amer. Heart Journ.*, 1930, **6**, 128.
 REBAUDI : *Monat. f. Geburtsch. u. Gynak.*, 1912, **XXXV.**, 681 (Ref. Matusoff-White).
 REICHE : *Klin. Woch.*, 1926, **37**, 1086 and 1711 (Ref. Schulte).
 RUGE : *Dermat. Woch.*, 1932, **XCIV.**, 278-286.
 SABRAZÈS and DUPÉRIER : *Arch. d. mal. d. cœur.*, 1909, **2**, 257.
 SCHARPF : *Frankf. Z. Path.*, 1909, **2**, 287 (Ref. Schulte).
 SCHLESINGER : *Syphilis und Innere Medizin*. 3 Teil. Wien., 1928 (Ref. Schulte).
 SCHULTE : *Zeit. f. Kreislauff.*, 1930, **XXII.**, 753.

BRITISH JOURNAL OF VENEREAL DISEASES

- SIEGMUND : *Zeit. f. Kreislauff*, 1929, **XXI.**, 389 (Ref. Schulte).
 STADLER : *Die Klink. d. Syphilit. Aortenerkrank*, Jena, 1912 (Ref. Stolkind).
 STOLL : *Journ. Amer. Med. Assoc.*, 1914, **63**, 1558.
 STOLKIND : *Brit. Journ. Dis. Child.*, 1920, **17**, 126.
 STRATHY, SMITH and HANNAH : *Lancet*, 1920, **I.**, 802.
 THOENES : *Ztschr. f. Kinderheilk*, 1922, **33**, 113 (Ref. Matusoff-White).
 THOREL : *Pathol. d. Kreislauff. Lubarsch-Ostertag's Erg.*, 1910, Abt. **II.**, **XIV.** (Ref. Stolkind).
 TRACHTENBERG : *Charkowski Med. J.*, **5**, 190 (Ref. Schulte).
 TURNBULL : *Tr. Med. Soc. Lond.*, 1911, **XXXIV.**, 390.
 VEEDER and JEANS : *Amer. Journ. Dis. Child.*, 1914, **8**, 283.
 VEEDER and JEANS : *Abt's Pediatrics*, 1924, **V.**, 613.
 VOEGTLIN, DYER and LEONARD : *Journ. Pharm. and Exp. Therap.*, 1925, **XXV.**, 297.
 VON ZETKOWSKY : *Diss. Inaug. Giessen.*, 1916 (Ref. Schulte).
 WARTHIN : *Am. Journ. Med. Sci.*, 1914, **147**, 667.
 WARTHIN : *Journ. Infect. Dis.*, 1916, **19**, 138.
 WARTHIN : *Am. Journ. Syph.*, 1918, **2**, 45.
 WARTHIN : *Journ. Infect. Dis.*, 1922, **30**, 569.
 WATERMAN : *Nedrl. Tijdschr. voor Geneesk.*, 1908, **I.** (Ref. Zentralbl. f. inn. Med., 1908, **XXIX.**, 910).
 WIESNER : *Zentralbl. f. alleg. path. u. path. anat.*, 1905, **16**, 822.
 WEISNER : *Frankf. Z. Path.*, 1910, **4**, 161 (Ref. Schulte).
 WIESNER and RACH : *Wien. Klin. Woch.*, 1907, **20**, 521.
 WILLCOX : *Lancet*, 1931, **II.**, **III**, 114.
 WILSON and MARCY : *Trans. Coll. Phys. Phila.*, 1907, **29**, 48 (Ref. Matusoff-White).
 WINTERNITZ : *Johns Hopkins Hosp. Bull.*, 1913, **24**, 212.
 ZIEDLER : *Diss. Inaug. Kiel.*, 1922 (Ref. Schulte).